PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference TV/12893.16	**FOR FURTHER ACTION** See Form PCT/IPEA/416	
International application No. PCT/CA2004/001724	International filing date *(day/month/year)* 22 September 2004 (22-09-2004)	Priority date *(day/month/year)* 22 September 2003 (22-09-2003)
International Patent Classification (IPC) or national classification and IPC IPC: ***A61K 36/00*** (2006.01), ***A61P 39/06*** (2006.01), ***A61P 29/00*** (2006.01), ***A23L 1/30*** (2006.01)		
Applicant PURECELL TECHNOLOGIES INC. ET AL		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 5 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. [X] *(sent to the applicant and to the International Bureau)* a total of 10 sheets, as follows:
      [X] sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      [ ] sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. 1 and the Supplemental Box.
   b. [ ] *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).
4. This report contains indications relating to the following items:
   - [X] Box No. I Basis of the report
   - [ ] Box No. II Priority
   - [X] Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - [ ] Box No. IV Lack of unity of invention
   - [X] Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - [ ] Box No. VI Certain documents cited
   - [ ] Box No. VII Certain defects in the international application
   - [ ] Box No. VIII Certain observations on the international application

Date of submission of the demand 20 July 2005 (20-07-2005)	Date of completion of this report 7 February 2006 (07-02-2006)
Name and mailing address of the IPEA/CA Canadian Intellectual Property Office Place du Portage I, C114 - 1st Floor, Box PCT 50 Victoria Street Gatineau, Quebec K1A 0C9 Facsimile No.: 001(819)953-2476	Authorized officer Kathleen Pound (819) 953-9757

Box No. I Basis of the report

1. With regard to the **language**, this report is based on:

[X] the international application in the language in which it was filed

[ ] a translation of the international application into , which is the language of a translation furnished for the purposes of:

[ ] international search (Rules 12.3(a) and 23.1(b))

[ ] publication of the international application (Rule 12.4(a))

[ ] international preliminary examination (Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report):*

[ ] the international application as originally filed/furnished

[X] the description:

[ ] pages 1, 3 to 10, 12 to 17 as originally filed/furnished

[X] pages* received by this Authority on

[X] pages* 2 and 11 received by this Authority on 23 December 2005

[X] the claims:

[ ] pages as originally filed/furnished

[ ] pages* as amended (together with any statement) under Article 19

[X] pages* 18 and 19 received by this Authority on 23 December 2005

[ ] pages* received by this Authority on

[X] the drawings:

[ ] pages as originally filed/furnished

[X] pages* 1 to 6 received by this Authority on 23 December 2005

[ ] pages* received by this Authority on

[ ] a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing.

3. [X] The amendments have resulted in the cancellation of:

[X] the description, pages 2 and 11 as originally filed

[X] the claims, Nos. 1 to 9 as originally filed

[X] the drawings, sheets/figs 1 to 6 as originally filed

[ ] the sequence listing *(specify):*

[ ] any table(s) related to sequence listing *(specify):*

4. [ ] This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

[ ] the description, pages

[ ] the claims, Nos.

[ ] the drawings, sheets/figs

[ ] the sequence listing *(specify):*

[ ] any table(s) related to sequence listing *(specify):*

* *If item 4 applies, some or all of those sheets may be marked "superseded."*

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The question whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

[ ] the entire international application

[X] claims Nos. 4 and 10

because:

[X] the said international application, or the said claims Nos. 4 and 10
relate to the following subject matter which does not require an international preliminary examination *(specify):*

Although claims 4 and 10 are methods of treatment of the human/animal body which this Authority is not required to examine under Rule 67.1 (iv) of the PCT, the written opinion has been established on the basis of the alleged effects of the purified thylakoids defined in claims 4 and 10.

[ ] the description, claims or drawings *(indicate particular elements below)* or said claims Nos.
are so unclear that no meaningful opinion could be formed *(specify):*

[ ] the claims, or said claims Nos. are so inadequately supported
by the description that no meaningful opinion could be formed *(specify):*

[ ] no international search report has been established for said claims Nos.

[ ] a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

[ ] furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

[ ] furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

[ ] pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b) and 13*ter*.2.

[ ] a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

[ ] the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

[ ] See Supplemental Box for further details.

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	None	YES
	Claims	1 to 11	NO
Inventive step (IS)	Claims	None	YES
	Claims	1 to 11	NO
Industrial applicability (IA)	Claims	1 to 11	YES
	Claims	None	NO

2. Citations and explanations (Rule 70.7)

Reference is made to the following documents:

D1: WO 01/49305 A2 (PURCELL, M.) 12 July 2001.

D2: WO 03/004042 A1 (ANDERSEN, A., et al.) 16 January 2003.

D1 discloses a thylakoid extract of the instant application, its anti-oxidative properties, compositions of said extract and it's use as a therapeutic in diseases and disorders that involve reactive oxygen species. The extract appears to be identical to that disclosed in the instant application. Furthermore, the use of the thylakoid composition as an enteral composition is also disclosed (page 61, line 5).

D2 discloses a thylakoid extract of the instant application, its anti-inflammatory properties, compositions of said extract and it's use as a therapeutic in diseases and disorders that involve inflammation. The extract appears to be identical to that disclosed in the instant application. Furthermore, the use of the thylakoid composition in the intestinal lumen is also disclosed (page 27, lines 19 to 21). Also, systemic formulations are disclosed on page 10, lines 18 to 20 which could presumably be administered orally. On page 10, line 25 to page 11, line 7, compositions of the thylakoid extract combined with other orally administered anti-inflammatory agents are disclosed.

NOVELTY: (Article 33(2) of the PCT)

Claims 1 to 11 are not considered to be novel under Article 33(2) of the PCT. Documents D1 and D2 disclosed the subject matter before the claim date. The use of the thylakoid extract of the instant application as an anti-oxidative and anti-inflammatory compound was known in the art as of the claim date, as shown in documents D1 and D2, respectively. Furthermore, the functionality of the extract in the digestive tract was also disclosed in D1 (page 61, line 5) and most notably experiment 11 on pages 27 and 28 of D2.

Given that the use of the thylakoid extract to treat diseases involving the formation of reactive oxygen species and inflammation is known, the claims are considered to lack novelty. Even if the claims are purported to differ from the art in that they offer an allegedly new route of administration, the use and form of the thylakoid extract remains the same. The applicant has not discovered a new use per se for the thylakoid extract. Thus the claims are not considered to define novel subject matter in view of documents D1 and D2. Furthermore, the carrier specified in claim 1 is not required for the oral composition, as specified on page 9 of the description. The addition of this non-essential feature to the claims does not render them novel over the prior art.

Continued in the supplemental box.

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**

Continuation of: Box V. 2. Citations and explanations

In the response of December 23, 2005 to the Written Opinion of this Authority, the applicants argued that document D1 does not disclose the oral administration of the thylakoid extracts of the instant application as "enteral" indicates intestinal delivery which does not necessarily occur via oral administration. However, it is the examiner's position that the admission of successful enteral use of the thylakoid extract teaches towards successful oral use as oral administration of a compound results in enteral use. Furthermore, there is nothing in document D1 to suggest that the enteral use could not be accomplished through oral administration.

Applicant further argued that the stomach is a significant barrier to oral administration, and the successful oral administration of the thylakoids is inventive. However, as the same thylakoid extract of the prior art was able to be successfully administered by gavage, the instant application indicated that the composition does not need to be different from that of the prior art in order to be active after passing through the stomach. Thus the instant application is not patentably distinct from that of the prior art.

Applicant also argued that document D2 does not disclose an oral route of administration or oral use. However the examiner maintains that document D2 applies to the claims for the same reasons as document D1: The thylakoid extract of the instant application is the same as that of the prior art, this same composition is effective after oral administration, and indications of successful use in the intestine and the absence of indications that the extract would not be useful orally are present in the prior art. The subject matter of the instant application is not patentably distinct from that of the prior art.

INVENTIVE STEP: (Article 33(3) of the PCT)

As claims 1 to 11 are not considered to be novel, they do not define an inventive step under Article 33(3) of the PCT.

INDUSTRIAL APPLICABILITY: (Article 33(4) of the PCT)

Claims 1 to 3 and 5 to 9 and 11 appear to have industrial applicability under Article 33(4) of the PCT, based on the function of the thylakoid extracts of the instant application as anti-oxidative and anti-inflammatory compounds. Although the methods per se defined in claims 4 and 10 relate to subject matter which this Authority is not obliged to examine under Rule 67.1 (iv) of the PCT, the use of the purified thylakoids referred to therein for treating or preventing disorders involving the formation of reactive oxygen species or inflammation appears to represent subject matter that has industrial applicability.

complexes that are located in thylakoids membrane.

Recently a dynamic and intact thylakoid membrane extract having both anti-oxidative and anti-inflammatory properties and its use in combination with other anti-inflammatory compounds have been described in International patent publication numbers WO 01/49305 and WO 03/004042, respectively. The anti-oxidative and anti-inflammatory properties of the thylakoid extract have been demonstrated in *in vitro, ex vivo, in situ* and *in vivo* studies. Specifically, the thylakoid extract has been shown to capture the noxious reactive oxygen species including singlet oxygen species and to modulate pro- and anti-inflammatory cytokines toward attenuation of inflammation.

In vivo, topical applications (direct application at site of injury) of the thylakoid extract have been shown to prevent or reduce the UV-induced skin damages in hairless mice and to decrease TPA-induced ear inflammation in rats and mice as well as preventing damage to intestinal mucosa induced by TNBS or DSS in rats. Also, intraperitoneal injection of the thylakoid extract has been shown to reduce carrageenan-induced paw oedema. However, today, no data has confirmed the potential use of the thylakoid extract as an oral anti-oxidative and/or anti-inflammatory agent.

The present invention relates to the use of a thylakoid extract as an oral therapeutic agent.

Three commercially available polymers were used for this study sodium alginate, carboxymethyl cellulose low viscosity (CMC1) and carboxymethyl cellulose high viscosity (CMC2). The complex PCT was given by PureCell Technologies inc.

PCT stability to compression

First of all, PureCell Technologies inc. PCT was compressed as such, with any excipient, in order to evaluate the capacity of PCT to preserve its biological activity, following compression. Tablets of 200 mg made from PCT only were obtained by dry compression at 1, 2.5 and 5 T in a Carver hydraulic press using a punch of 9 mm diameter. The obtained tablets were broken down to powder and sent to PureCell Technologies inc. where the complex activity was tested.

PCT stability to compression in presence of polymeric excipients

Tablets of 200 mg based on, one of the three polymers (alginate, CMC1 or CMC2) containing 20, 40 or 60% of PCT were obtained by dry compression at 2.5 T in a Carver hydraulic press using a punch of 9 mm diameter. The obtained tablets were sent to PureCell Technologies inc. where the complex activity was tested.

Tablet behavior in simulated gastro-intestinal fluid

Two series of tablets of 200 mg were realized, one composed of one of the three polymers (alginate, CMC 1 or CMC2) without the PCT and the other based on one of the three polymers containing 20, 40 or 60% of PCT. Tablets were obtained by dry compression at 2.5 T in a Carver hydraulic press with a 9 mm diameter punch.

The comportment of tablets was tested in simulated gastric fluid

Claims

1. The use of purified thylakoids and a carrier in the making of an oral composition for treating or preventing a disease or disorder involving the formation of reactive oxygen species or inflammation, with the proviso that the carrier does not essentially consists of water, physiological saline or propylene glycol.

2. The use of purified thylakoids in the making of an oral composition for preventing oxidative damages to components of the composition.

3. The use of claim 1 or 2, wherein the oral composition is food or food supplement.

4. A method for treating or preventing a disease or disorder involving the formation of reactive oxygen species or inflammation, in a subject, which comprises the step of orally administering an effective dose of purified thylakoids.

5. An oral composition comprising purified thylakoids and a carrier for oral ingestion or oral administration, with the proviso that the carrier does not essentially consists of water, physiological saline or propylene glycol.

6. The oral composition of claim 5, which is food or food supplement.

7. The oral composition of claim 5, which is a medication selected from the group consisting of a pellet, encapsulated granules and encapsulated powder.

8. The oral composition of claim 5, wherein the carrier is present in an amount of 0.01 % to 95% (w/w).

9. The use as defined in claim 1, 2 or 3, wherein the purified thylakoids are present in an amount which achieves a dosage of 0.1 to 10 mg per Kg of a subject's body weight.

10. The method as defined in claim 4, wherein the purified thylakoids are present in an amount which achieves a dosage of 0.1 to 10 mg per Kg of a subject's body weight.

11. The composition as defined in any one of claims 5 to 8, wherein the purified thylakoids are present in an amount which achieves a dosage of 0.1 to 10 mg per Kg of a subject's body weight.

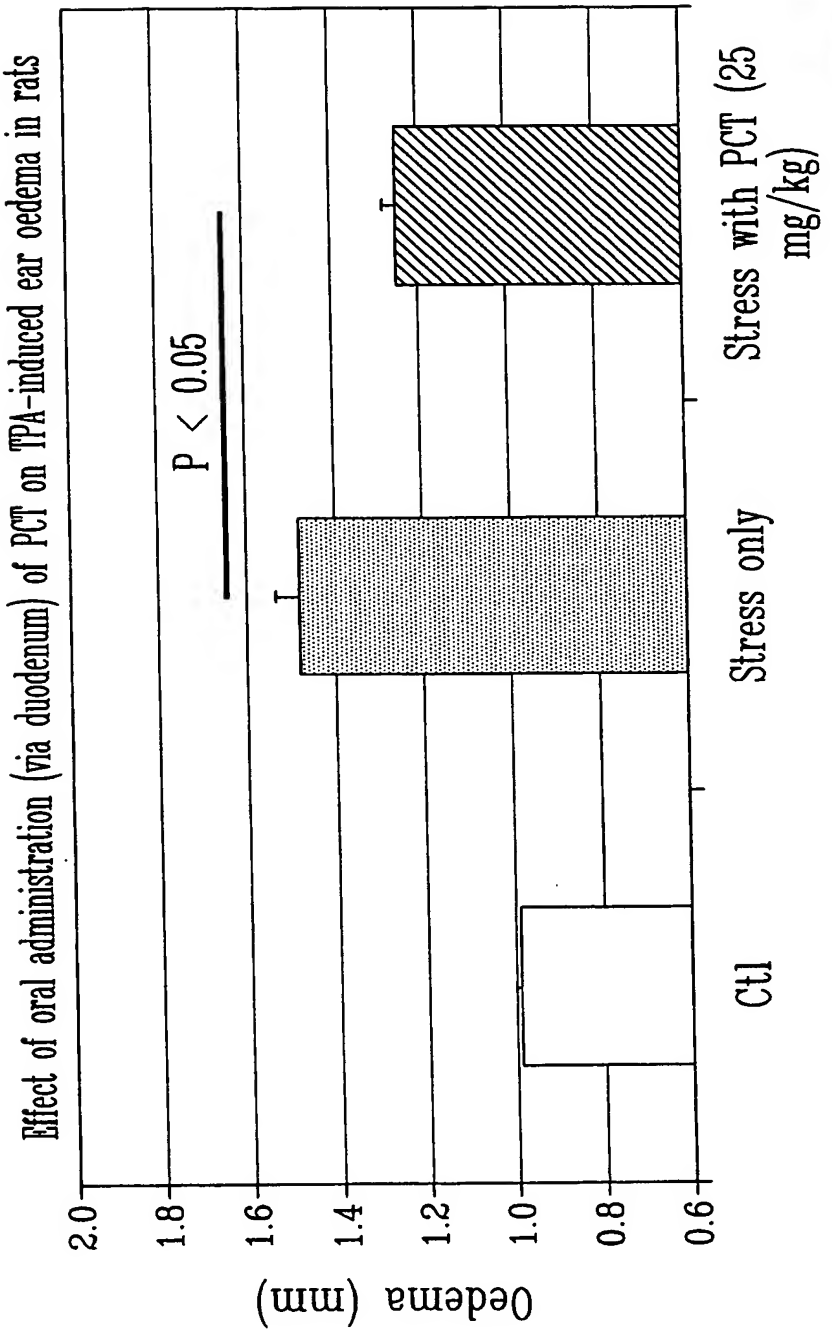
Effect of oral administration (via duodenum) of PCT on TPA-induced ear oedema in rats
Oedema (mm)
2.0
1.8
1.6
1.4
1.2
1.0
0.8
0.6
P < 0.05
Ctl
Stress only
Stress with PCT (25 mg/kg)

Fig. 1

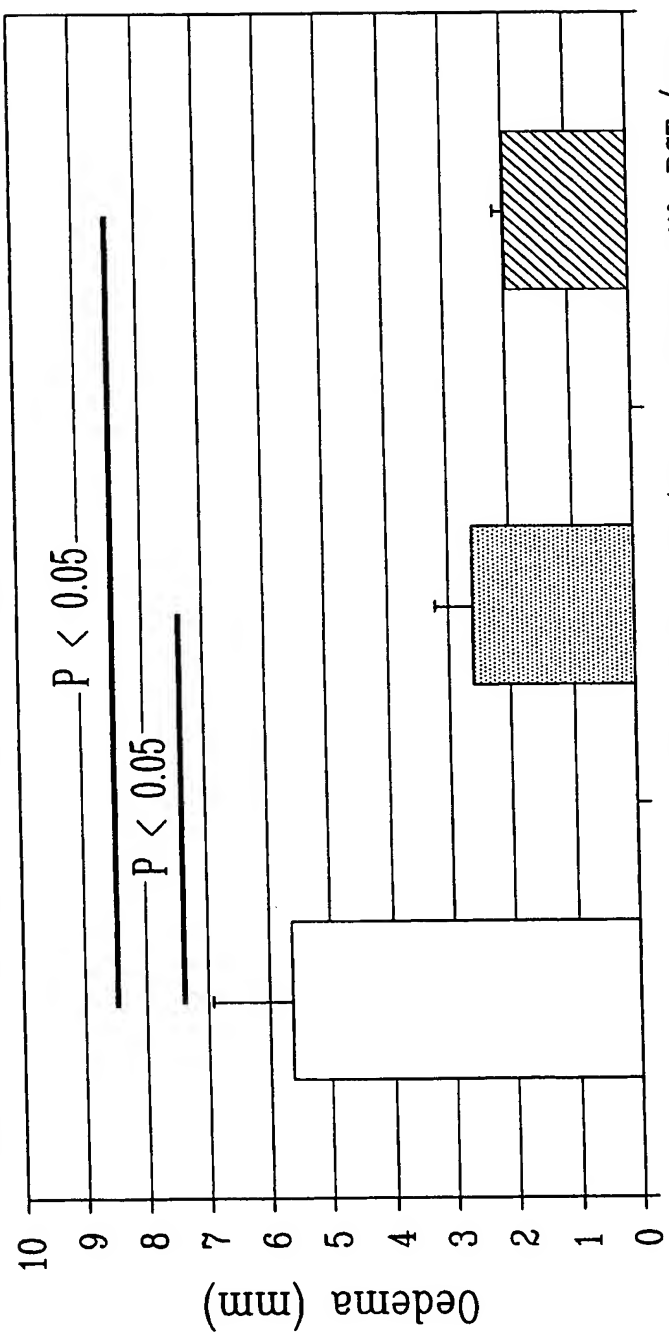
Effect of oral administration (duodenum and gavage) on carrageenan-induced paw oedema
Oedema (mm)
0
1
2
3
4
5
6
7
8
9
10
P < 0.05
P < 0.05
Stress only
Stress with PCT (duo 25 mg/kg)
Stress with PCT (gav 25 mg/kg)

Fig-2

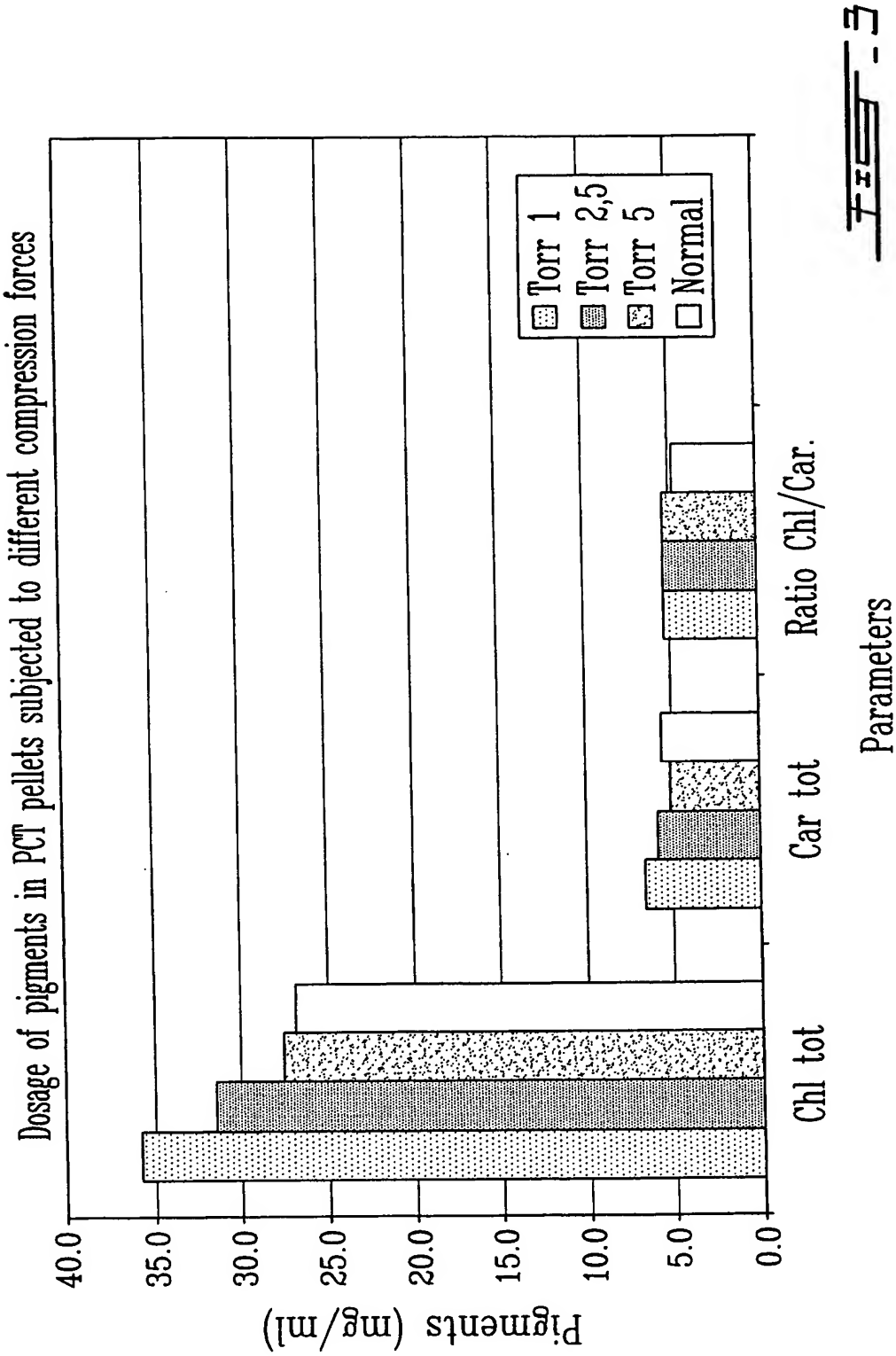
Dosage of pigments in PCT pellets subjected to different compression forces
Pigments (mg/ml)
40.0
35.0
30.0
25.0
20.0
15.0
10.0
5.0
0.0
Torr 1
Torr 2,5
Torr 5
Normal
Chl tot
Car tot
Ratio Chl/Car.
Parameters

Fig - 3

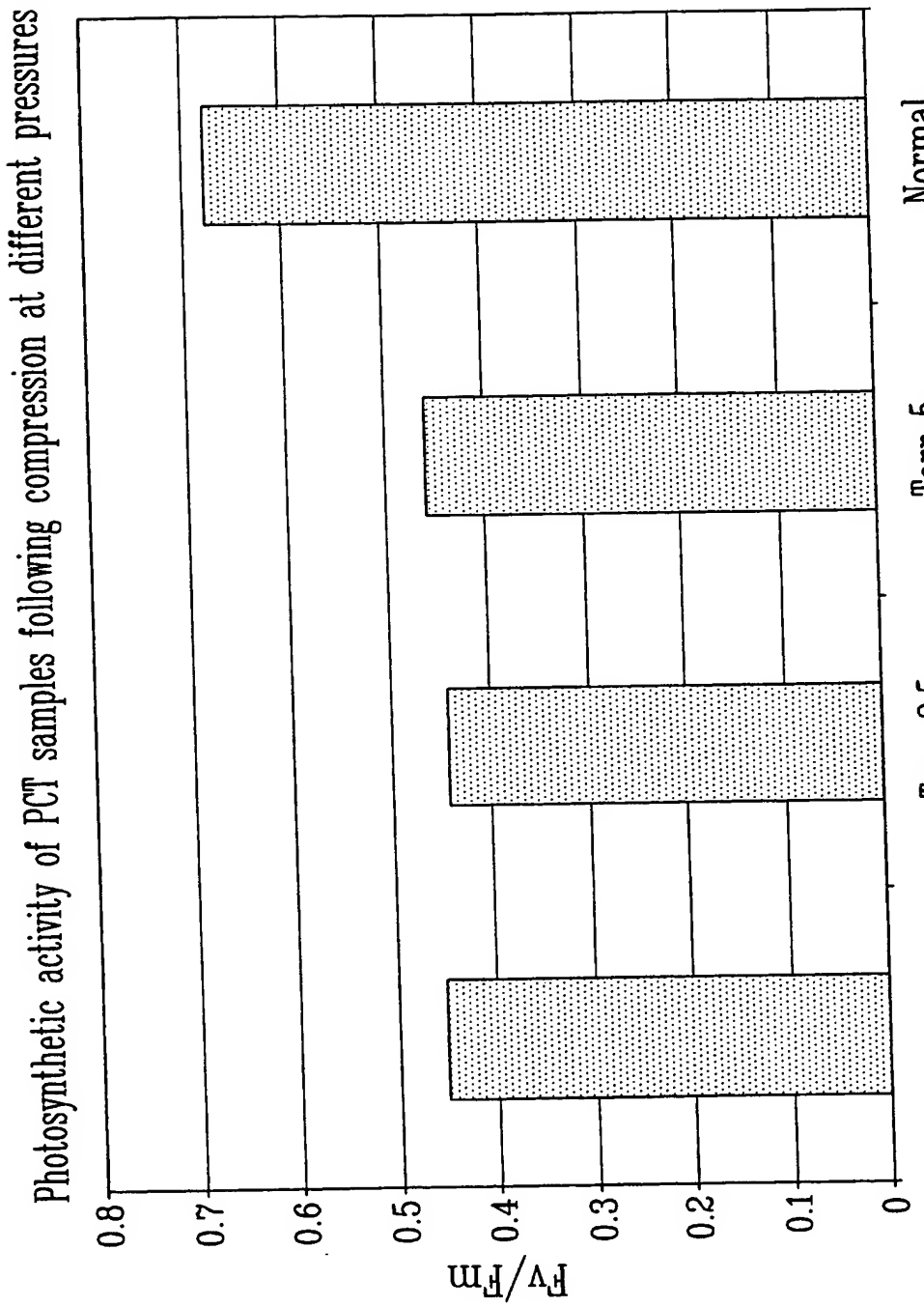
Photosynthetic activity of PCT samples following compression at different pressures
Fv/Fm
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
Normal
Torr 5
Torr 2,5
Torr 1
PCT Samples

Fig - 4

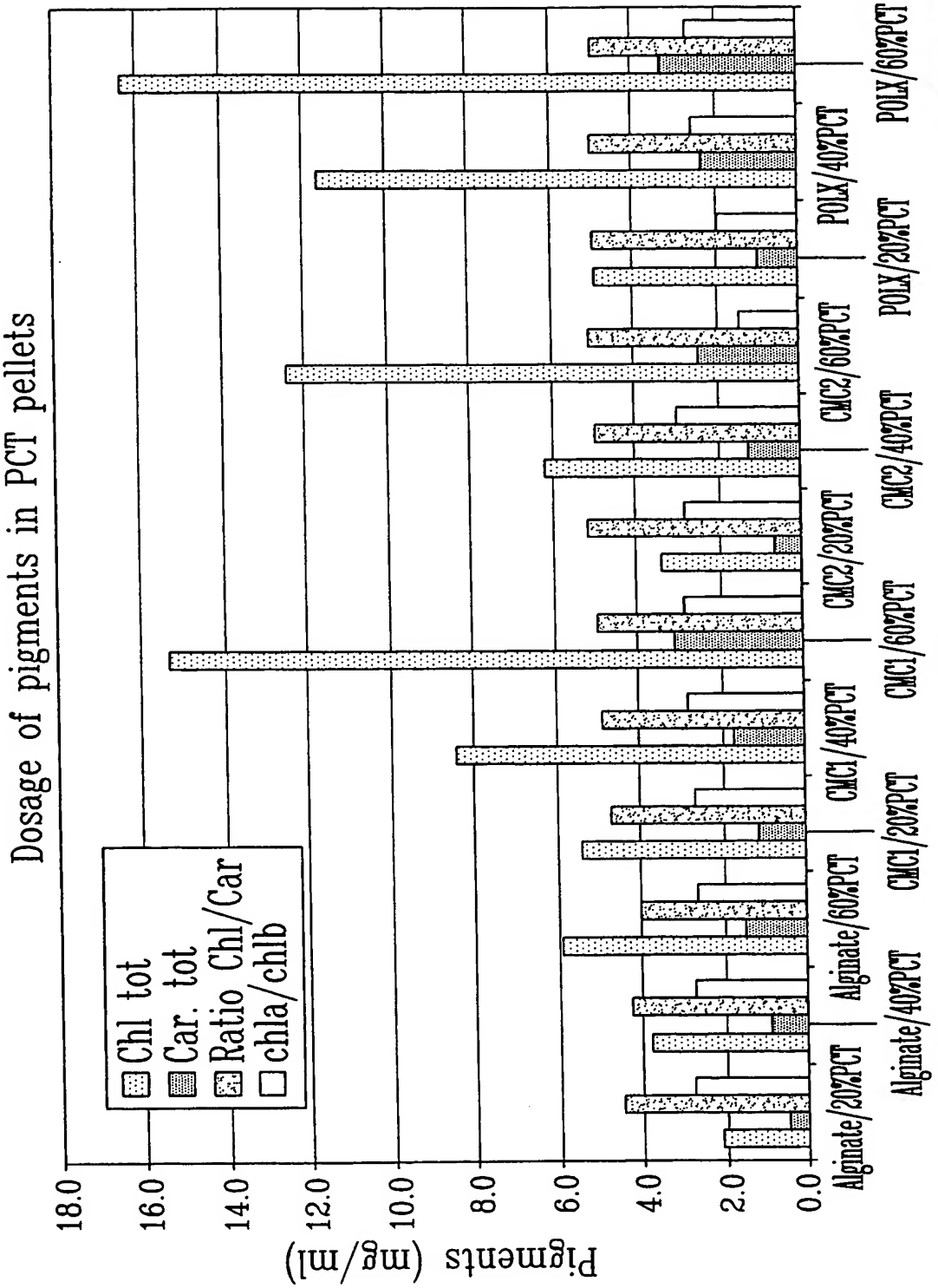
Dosage of pigments in PCT pellets
Chl tot
Car. tot
Ratio Chl/Car
chla/chlb
Pigments (mg/ml)
18.0
16.0
14.0
12.0
10.0
8.0
6.0
4.0
2.0
0.0
Alginate/20%PCT
Alginate/40%PCT
Alginate/60%PCT
CMC1/20%PCT
CMC1/40%PCT
CMC1/60%PCT
CMC2/20%PCT
CMC2/40%PCT
CMC2/60%PCT
POLX/20%PCT
POLX/40%PCT
POLX/60%PCT
PCT Pellets

Fig-5

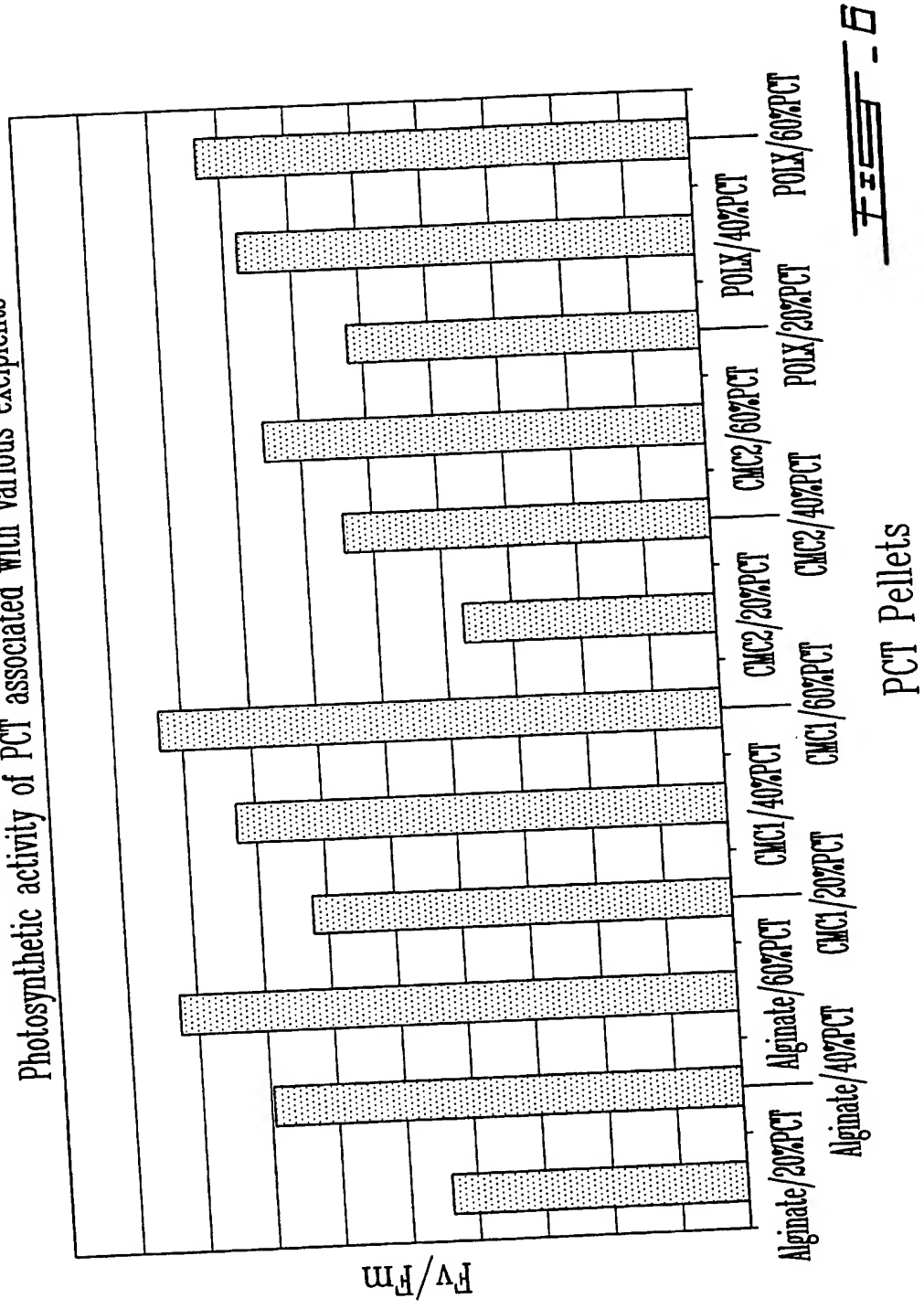
Photosynthetic activity of PCT associated with various excipients
Fv/Fm
Alginate/20%PCT
Alginate/40%PCT
Alginate/60%PCT
CMC1/20%PCT
CMC1/40%PCT
CMC1/60%PCT
CMC2/20%PCT
CMC2/40%PCT
CMC2/60%PCT
POLX/20%PCT
POLX/40%PCT
POLX/60%PCT
PCT Pellets

Fig - 6